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Synopsis

RADIOLOGY IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE

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The majority of congenital malformations may be differentiated by study of information obtained on physical examination, electro-cardiograms, X-ray and a fluoroscopic examination.

In a small percentage of cases, however, the more recent technique of angiocardiography and heart cathetrization are proving to be valuable in diagnosing some of the more difficult cases.

Fluoroscopy has more advantages than X-ray in that it allows examination of the patient in numerous positions and brings to light any artefacts produced by moving the heart and shoulders. Barium swallows give an indication of the relationship of the esophagus and heart.

Various positions of examination gives different information about the heart and vessels:

1—the antero-posterior position shows the size and shape of the heart and great vessels,

2—the left anterior oblique position shows the relative size of the ventricles,

3—the course of the aorta and the size of the left auricle may be determined from the right anterior oblique position.

The cardiac silhouette is considered to be of little help in the infant.

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Office Procedure in the Diagnosis of Hematologic Disorders

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INTRODUCTION

It is not generally appreciated that a practitioner, with a minimum of equipment, some knowledge and a fair amount of patience can make in his office a reasonably neat diagnosis of a blood dyscrasia. The categorization of abnormalities of the peripheral blood is not strictly an exercise for a hospital laboratory, if a few inexpensive tools and a knowledge of how to use them are at hand.

This article will make no attempt to classify abnormalities of the hemopoietic system. Rather, the purpose is to draw to the reader's attention some basic facts, the appreciation of which may contribute towards making the practice of medicine a little less hum-drum and perhaps a little more exciting. Furthermore, one may say that treatment can scarcely be rational without a precise diagnosis. Hence the necessity for a definite diagnosis, if at all possible, is self-evident. Polypharmacy as it stands today may seem superficially to have simplified these problems but it has, in fact, introduced many new ones, for without any idea of the specificity of a response one may still be in doubt about the exact nature of the disease which he is treating.

It is perhaps superfluous to mention the importance of an adequate history, but it is really a paramount essential. For example, if one is dealing with an anemia, he must know whether blood loss has been occurring; whether the diet has been adequate; whether there may be associated infection, neoplasm, liver or kidney disease; whether potentially harmful drugs have been ingested; whether a harmful exposure to chemicals may have occurred.

Physical examination is equally important. One seeks especially for enlarged lymph nodes, bone tenderness, petechiae, or any peculiar skin lesions, jaundice, enlargement of the liver and/or spleen, and, of course, any other palpable masses. The old dictum about the absolute crime of not inserting a finger into the rectum may be mentioned here.

Actually the diagnosis of an hematologic disorder is most often, in the final analysis, a laboratory procedure. One can only make a presumptive diagnosis as a rule, without laboratory aid. Herewith then, will be described office laboratory procedures which can be quite definite.

(1) Hemoglobin Estimation

The methods which are used in the office of a busy practitioner must of necessity be simple and ideally not involve the acquisition of expensive apparatus. Estimations of hemoglobin level done by the Tallqvist or Sahli method are in such a category, but the important feature to be remembered is that the range of accuracy may be as poor as $\pm$ 15 to $\pm$ 30%. Accordingly, a mild anemia (10.0 Gm.) may be read as 8.5 Gm. (a fairly severe anemia) or as 11.5 G.m. (a barely borderline anemia in the female), using the Sahli method. If the Tallqvist method is used a mild anemia (10.0 Gm.) may be read as 13.0 Gm. (normal in the female) or as 7.0 Gm. (a severe anemia). Using the Spencer colorimetric method a greater range of accuracy ($\pm$ 5 to $\pm$ 10%) may be obtained.

For the optimal accuracy photoelectric methods must be employed. This apparatus may be temperamental and is subject to error too, but a photoelectric machine will deliver with an accuracy of ± 1 to $\pm$ 2%. *The normal range of hemoglobin is 12 - 16 Gm. in the female, and 14 - 18 Gm. in the male.* This terminology is the accepted and certainly the logical one at the moment. Since the normal hemoglobin has a range it seems quite unscientific to select one value as representing 100%. In other words, anything between 14 and 18 Gm. in the male is 100%. The reporting of hemoglobin in percentage, then, has little to recommend it, and one rarely sees this done now.

(2) Red Cell Counts

These are mentioned simply to condemn them. Such counts are most difficult to do with a reproducible accuracy. To perform a quite accurate count, two pipettes with balanced correction factors and two counting chambers must be used. If inaccurate red cell counts are used for the calculation of indices (e.g. color index), the error is compounded and the physician may be severely mislead, but there is, of course, a real place for accurate red cell counts on occasion. However, as an office procedure they have nothing to recommend them.

(3) Hematocrit (volume of packed red cells)

It is unlikely that an adequate centrifuge will be available in the office of a practicing physician for the performance of this test. The ordinary centrifuge which is used for spinning urine must never be used. A speed of somewhere between 2500 and 3000 r.p.m. is necessary for maximum packing of the red cells in the Wintrobe hematocrit tube. These speeds cannot be obtained except with centrifuges which are built for the job.

The reproducible accuracy with which hematocrits can be performed is greatly in favor of the routine use of this test. In addition, one can examine the color of the plasma and make a rough estimate of the level of white blood cells and platelets. *The normal range is 47.0 $\pm$ 7.0% in the male and 42.0 $\pm$ 5.0% in the female.*

(4) White Cell Count

A white cell count is simply done and can be done accurately if the minimum of skill and care are used. This should be looked upon as an essential part of a complete examination. *The normal range is 5,000 - 10,000 per cu. mm.*

(5) Examination of a Smear of Peripheral Blood

A drop of fresh blood (from the fingertip or ear lobe) evenly and thinly spread on a clean glass slide (or preferably on a clean cover glass) and well-stained, is without doubt the most important single test available for the assessment of the status of the cellular components of the blood. From it, one can gain information on the character of the red cells—whether they are normal in size and shape, whether their hemoglobin content is normal and whether immature forms are present. On this observation depends mainly the selection of the proper agent for treatment. If the red cells are small and pale, the anemia is likely due to chronic blood loss. Immediately, an explanation for this must be sought. Ferrous sulfate by mouth will usually be effective, unless the blood loss is very rapid or unless iron cannot be absorbed from the gastro-intestinal tract. (This latter situation is a rare one indeed.) If the red cells are large, the bone marrow must be examined, for one may be dealing with a liver principle deficiency anemia, in which case, the marrow will be megaloblastic. If the red cells are normal in size and shape and anemia is actually present a search must be conducted for such things as chronic infection, uremia, acute blood loss, neoplasm,

myxedema, etc. If immature forms are present, causes of rapid blood formation must be sought for. By immature red cells one means nucleated forms, stippled forms and large bluish-grey forms. These last named cells are called polychromatophilic red cells and they are likely reticulocytes. In order to both identify these cells as reticulocytes and to count them, supravital stains may be used. This is not as a rule an office procedure, but it could be. The important thing to appreciate is that the routine smear would give one a lead toward further investigation which can then be ordered for a legitimate reason.

Red cells which are small and lack the normal central zone of pallor are called spherocytes. The finding of many of these on smear may mean a hemolytic anemia of either the acquired or congenital type. In the latter type they are apt to be much more numerous. The recognition of such cells then leads one to rational additional investigation.

As well, one may gain information on the leucocyte picture. A differential count of at least one hundred white blood cells will give the answer on an abnormal preponderance of any of the particular types of leucocytes and, even more important, will give information on whether or not any immaturity of granulocytes is present. The presence of granulocytes younger than the band or stab form must never go unexplained. The differential then, when paired with the total white count, will be the deciding features, not only in making a diagnosis of leukemia but in categorizing it.

Also from the smear of peripheral blood the adequacy of platelets may be appraised. If many platelets are seen, they can be said simply to be adequate numerically. If they occur in clumps, it is almost certain that their number is normal. Occasionally giant forms are seen. These are abnormal and may mean a functional inadequacy. Platelet counts are difficult to do as an occasional procedure and are, of course, not to be recommended as an office exercise. Clearly, if their numbers are adequate on the smear, a count is quite superfluous.

(6) Bleeding Time, Clotting Time, Capillary Fragility

If the patient presents a problem in abnormal bleeding, in addition to the evaluation of platelets, the physician may perform three simple tests — bleeding time, clotting time and capillary fragility. These, along with their rationale, have been dealt with by Dr. Meltzer in a separate paper in this issue of the Journal.

(7) Sedimentation Rate

The sedimentation rate which is normally looked upon as an index of tissue injury is increased actually because of an elevation in plasma globulins and/or plasma fibrinogen. Hence, it may be applied to hematologic diseases which do have changes in serum proteins. Striking elevations of serum globulin are seen usually in multiple myeloma (not a rare disease if it is kept in mind!) and lesser increases may be seen in Hodgkin's Disease and lymphocytic leukemia. Anemia itself has some accelerating effect on the fall of red cells, but if the Westergren method (which is the common one) is used, one does not need to correct for the degree of anemia. If the Wintrobe tube is used (and this is extremely convenient if a hematocrit is also going to be performed), correction curves have been developed to adjust for the degree of anemia. But it seems to be attempting to introduce quite a degree of accuracy into a crude test, and most authorities will not bother with correcting for anemia. At best, the erythrocyte sedimentation rate is only a screening test and its non-specificity makes it of limited value indeed in assessing the hematologic status of the patient.

(8) Bone Marrow Aspiration

The aspiration of bone marrow (from the sternum, iliac crests or posterior spinous processes) is clearly an office procedure from the technical point of view and it carries little or no risk. The most important part of this procedure, however, is the preparation of the smears and their interpretation. These latter exercises require some experience, so I am not in favor of bone marrow aspirations being done by practitioners who are not in a position to interpret what they see. Furthermore, some help may be gained from actually observing the events during the aspiration; the ease with which the bone was penetrated; the occurrence of suction pain; the presence of "chunks" of bone marrow in the aspirate. If the person who is asked to make a diagnosis has not performed the aspiration, I think his position is a little more difficult. In addition, it should be clearly appreciated that an appraisal of bone marrow aspirate is in no way a substitute for meticulous scanning of a film of peripheral blood. These examinations are simply complementary. I know of no contra-indications to bone marrow aspiration. One often hears that this procedure must not be done in the face of a bleeding tendency. There is no added risk in a patient who is bleeding, for most any bleeding from a hole created by a #18 needle can be controlled by manual pressure for several minutes.

Conclusion

In conclusion, it can be said that in the past fifteen years a considerable body of information has been accumulated relating to the blood dyscrasias. The utilization of these facts has removed therapy from the metaphysical sphere and placed it on a firm factual foundation. Not all blood dyscrasias are amenable to specific therapy for, very often, their etiology is unknown; hence no specific therapy is available. Here such supportive measures as blood transfusion may be quite justified and, indeed, may be the only therapeutic agent; but when a dyscrasia can be accurately categorized and a specific agent is available for its treatment, this agent should be used, and preferably used alone. The need for precise diagnosis is surely obvious and it seems to me that the practicing physician should be in a position to make such a diagnosis. At this point it might be justifiable to make a plea for diagnosis before any therapy is given, for often times after some treatment has been administered, even in small amounts, a precise diagnosis is extremely difficult or impossible.

With the above laboratory procedures one can do a great deal toward making a diagnosis of an abnormality of the peripheral blood. The practicing physician will get a greater thrill out of his labors and the patient will certainly benefit greatly, if the above-listed examination can be carried out and properly interpreted.

Leukemia

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INTRODUCTION

The most important single step in the diagnosis of leukemia is the microscopic examination of the stained blood film. The importance of this simple routine laboratory procedure cannot be stressed too strongly. However, many of these patients will be seen at a time when the hematologic findings do not give an immediate and effortless diagnosis. It should be emphasized, therefore, that these diseases are to be known by their entire natural history rather than by the few facts concerning their clinical pathology.

Definition

Leukemia is a disease of unknown etiology, which follows a progressive course that is individually variable but always fatal.

The acute and chronic forms of leukemia are distinguishable primarily by their duration and the degree of immaturity of the predominating cells, the acute form having the more rapid course with its cells being the more immature.

The leukemias are most conveniently classified according to the predominating types of cells.

I. Chronic leukemia
   a. Myelocytic
   b. Lymphocytic

II. Acute leukemia
   a. Myeloblastic
   b. Lymphoblastic
   c. Monocytic

The Nature of Leukemia

Leukemia is a disorderly, nonfunctioning overgrowth of myeloid or lymphoid cells, that is invariably fatal, and in these respects it resembles a malignant neoplasm.

A minority opinion is that it belongs to the dim borderline between inflammation and neoplasm.

Age and Sex Incidence

The acute and chronic forms of leukemia may occur in either sex at any age. However, the maximum incidence is shown below:

Type	*Age*
Acute leukemia	under 5 years
Chronic myelocytic	25 - 45 years
Chronic lymphocytic	45 - 60 years

Sex Incidence
M/F* : : 1/1
M/F : : 3/2
M/F : : 3/1

*M/F—Male/Female Ratio

Pathology

The essential feature of leukemia is a neoplastic proliferation of leukoblastic tissue resulting in a great increase in the white cells of the blood and cellular infiltration of organs. Occasionally, there is a proliferation of white cells in the tissue but they fail to appear in the blood stream, a condition called "aleukemic leukemia".

In chronic myelocytic leukemia there is a myeloid hyperplasia which largely crowds out the erythroblastic tissue. The spleen becomes enormously enlarged and firm, and may fill the entire abdomen. The liver is moderately enlarged; lymph nodes are usually normal in size.

In chronic lymphocytic leukemia the lymph nodes all over the body are enlarged and their normal microscopic architecture is replaced by a diffuse mass of lymphoid cells. Other lymphoid tissue is similarly affected. The spleen is usually moderately enlarged. The hyperplastic bone marrow is composed largely of lymphoid cells.

In the acute forms, the infiltrating cells are "blast" forms, but otherwise the infiltration in various tissues throughout the body is similar to that observed in the chronic leukemias. In addition, there is anemia and a hemorrhagic tendency due to thrombocytopenia.

CHRONIC MYELOCYTIC LEUKEMIA

Clinical Features

The onset is insidious. Frequently the initial complaints are weakness, pallor, palpitation and dyspnea, which are attributable to the slowly advancing anemia. There may be a fullness and dragging sensation in the abdomen due to the great splenic enlargement. Fever, of intermittent or remittent type, may be an early symptom. During acute exacerbations, and as a late feature, hemorrhages may occur under the skin, from the uterus, kidneys, bowels, or into the retina or middle ear.

These symptoms become more pronounced as the disease progresses.

Physical Examination

The general appearance of the patient varies widely depending upon the severity of anemia which is present.

1. Spleen is characteristically much enlarged, extending across the midline and reaching below the umbilicus.
2. Liver is usually palpable, and may become enormous.
3. Lymph nodes may occasionally be slightly enlarged, but remain discrete.
4. There may be purpuric hemorrhages under the skin.
5. As leukemic infiltrations may present in almost any tissue of the body, the possible complications are many; for example:
   i) retinal hemorrhages and leukemic infiltrations.
   ii) bluish grey, elevated nodules in the skin.
   iii) destruction of bone.
   iv) deafness by hemorrhage or leukemic infiltration in the inner or middle ears.
   v) hemorrhages or tumor-like infiltrations in the central nervous system.
   vi) hematuria.
   vii) gastrointestinal tract hemorrhages.

Blood Examination

1. R.B.C.: There is a moderate but slowly increasing anemia of normocytic and normochromic type; nucleated red cells may be found.
2. W.B.C.: Total count is 100,000 to 500,000 per cubic millimeter, or more. The myelocyte is the predominant cell, but more primitive forms are seen in the terminal stages or in the blast crisis of leukemia.
3. Platelets: Most frequently there is a slight increase in the blood platelets, or in some instances the numbers may be reduced to a marked degree.

If it is remembered that the white cell count, the red cell count, and platelet count may each approach 1,000,000, some

of the principal features of the blood picture may be recalled.

Prognosis

Spontaneous remissions lasting from months to years, have been reported, but all cases are invariably fatal. About 50% of chronic myelocytic leukemia patients die in an acute phase. The mean survival time is generally reported to be between two and three years from the time of diagnosis.

The terminal stage is indicated by:

i) increased myeloblasts in peripheral blood,

ii) marked anemia,

iii) hemorrhages,

iv) failure to respond to roentgen therapy.

CHRONIC LYMPHOCYTIC LEUKEMIA

Clinical Features

The onset is insidious. The clinical manifestations of anemia—pallor, weakness, fatigue, dyspnea and palpitations—may be the presenting symptoms. Frequently the patient observes a painless, nontender lymph node in the neck, axilla or groin. Less frequently, itchy red skin caused by leukemic infiltration, or a hemorrhagic tendency may be the presenting complaint.

Physical Examination

Again, the general appearance of the patient depends upon the degree of anemia which is present.

1. The lymph nodes of cervical, axillary and inguinal regions are most frequently enlarged. They are firm, rubbery, discrete and painless. Some nodes may attain the size of a hen's egg, and it is not uncommon to have them spontaneously diminish in size. The condition of the superficial lymph nodes is not always a reliable indication as to the presence or absence of general lymphoid hyperplasia, for the deep nodes (abdominal and mediastinal) may be greatly enlarged though the superficial ones are barely palpable.
2. The firm non-tender edge of the spleen is most often palpable 7 to 8 cm. below the left costal margin, but never is a huge size attained.
3. The liver is usually moderately enlarged.

Blood Examination

1. R.B.C.: Anemia is not nearly as marked as in chronic myelocytic leukemia. But as the disease progresses, a normocytic, normochromic anemia develops and becomes more severe.
2. W.B.C.: Only the lymphoid cells are increased, and may form as much as 90% of the average total count of 50,000 to 100,000.
3. Platelets: The platelet count is characteristically moderately decreased, but occasionally there is a great fall or complete disappearance of platelets resulting in bleeding.

PROGNOSIS

The prognosis is better than in chronic myelocytic leukemia. The average length of life in patients with chronic lymphocytic leukemia is usually given as 3.5 years from the onset of symptoms. Some live for 5 or 10 years and undoubtedly a small percentage go into spontaneous remission for several months or years, but eventually the terminal stage of the disease is reached. About 15% of chronic lymphocytic leukemia patients die in an acute phase.

ACUTE LEUKEMIA

Probably six types of acute leukemia have been recognized, but for practical purposes they may be considered as a group, since the clinical features and treatment are similar in all types. Frequently the predominating type of primitive cell cannot be positively identified.

Clinical Features

Usually the clinical onset is abrupt, and is often considered to be due to an upper respiratory infection. There is fever, general malaise leading to prostration, and a rapidly advancing anemia. Mainly because of thrombocytopenia, epistaxis, spongy bleeding gums, purpura and other hemorrhagic manifestations are common. Sore throat and necrotic ulcers in the mouth or pharynx are frequent. Lymph nodes may be enlarged; the spleen and often the liver are enlarged in terminal stages.

Blood Examination

1. R.B.C.: There is almost always a profound anemia, in which the total red cells are 1,000,000 or less, per cubic millimeter.
2. W.B.C.: The distinguishing feature is the presence in the blood of a large number of mononuclear, nongranular primitive white cells. The total count may be as low as 2,000, but usually is increased to 20,000 or 30,000.
3. Platelets: Thrombocytopenia is an invariable feature, in fact, the platelets are virtually lacking.

Prognosis

The condition is invariably fatal, usually within eight weeks of onset. Occasionally spontaneous remissions occur and last up to six months, and in a few rare cases, up to two years.

TREATMENT OF LEUKEMIAS

Doubts are beginning to appear in the minds of some authorities as to whether treatment of the active case will actually prolong life. However, statistics relating to a large series of cases will never point up the remarkable results which take place occasionally in some individual cases. It is generally accepted that specific therapy should be instituted when definite symptoms appear or when the disease enters a more active phase, and not necessarily when the diagnosis is made.

Dr. Osgood's method of treating the patient as soon as leukemia is diagnosed using "titrated" P^{32} at regular intervals, the dosage being governed by the induced response of the patient, has been the object of much interest. Osgood reports mean survival time of slightly over four years using "titrated" therapy, in contrast to mean survival time of slightly over two years using standard therapy.

Certainly therapy of chronic lymphocytic leukemia should be subtle and unobtrusive. This is particularly true in asymptomatic cases in the older age group discovered accidentally. Here no therapy is by far the best therapy unless the disease gets out of hand. Then and only then—and here Dr. Osgood disagrees—should therapy be instituted.

Treatment of Chronic Leukemia

It is most important that the differential diagnosis be accurate, because the treatment of chronic forms is entirely different from that of the acute forms.

The treatment of chronic leukemia of all types may be conveniently grouped under radiation, chemical agents, and supportive measures.

1. *Radiation*: Roentgen rays, radium, radioactive isotopes may be used.

i) The use of roentgen rays is the most satisfactory. X-rays may be directed on a regional basis to enlarged spleen or lymph nodes, or by generalized "spray" radiation. In chronic lymphocytic leukemia the localized form of treatment is preferable. After a series of treatments, the leukocyte count may fall to nearly normal, and further radiation may not be required for many months. As time goes on, the intervals between treatments become shorter and eventually the condition will become refractory and death ensues.

Irradiation should not be used in acute leukemia at any time. It may be safely employed in "aleukemic" patients when the leukocyte count is subnormal in the beginning.

ii) Radioactive phosphorus is said to be as effective as roentgen radiation in the myelocytic type, but less effective in lymphocytic leukemia. The radioactive isotope P^{32} has a half-life of about fourteen and one-half days. It is given either by mouth or by injection and localizes in the marrow, where overdoses cause thrombocytopenia, leukopenia and anemia. If the facilities are available, it is a convenient method of treatment, and no irradiation sickness results. It is of no value in acute leukemia.

2. *Chemical Agents*:

i) Arsenic and benzene:

These have largely been replaced by newer, more effective agents.

ii) Urethane (ethyl carbamate):

Satisfactory and sometimes fairly long-lasting remissions can be induced in patients with chronic myelocytic leukemia, but it is of little benefit in the treatment of chronic lymphocytic or acute leukemias. To be effective, therapy with urethane must be persevered. Enteric coated tablets are often passed unchanged; it is best given as a syrup with meals, in dosage of 2 to 4 grams. Urethane is not generally used.

iii) Nitrogen mustard:

The use of nitrogen mustard is disappointing in the treatment of chronic leukemias. It is of more use in treating Hodgkin's disease.

iv) T.E.M. (triethylenemelamine):

T.E.M. is probably the treatment of choice in chronic lymphocytic leukemia. Since the response of the individual patient varies tremendously, T.E.M. must be cautiously instituted with a single dose of 1 to 2 milligrams, and the hematological details be closely followed for two or three weeks. Some patients have a marked decrease in leukocyte count following the first dose. T.E.M. is most suitable when the platelet count is not depressed, because excessive doses cause hemorrhagic tendencies due to thrombocytopenia. It is of very little value in chronic myelocytic leukemia, and in acute leukemia.

v) Myleran:

This cytotoxic agent exerts a retarding effect on any tissue, but a relatively selective retardation of granulopoeisis. It is effective in the treatment of myelocytic leukemia. Given in

oral daily doses of 4 milligrams, it produces general improvement in the patient's well-being, increase in appetite and weight gain; definite reduction in size of spleen and liver, as well as decreased numbers of granular leukocytes in peripheral blood. The number of lymphocytes in peripheral blood is not influenced. Myleran is completely ineffective in acute leukemia, chronic lymphocytic leukemia, and chronic myelocytic leukemia during the outpouring of myeloblasts.

3. *Supportive Measures*:

i) The prevention and treatment of minor infections.

ii) Adequate nutrition and vitamins. Folic acid is definitely contraindicated.

iii) Bed rest is indicated only until there has been a remission of fever. Otherwise patients may be as active as their individual capacities permit.

iv) Anemia: 1. The anemia associated with chronic myelocytic leukemia almost uniformly improves when the leukemic process is under control. Transfusions are rarely required.

2. The acquired hemolytic anemia associated with chronic lymphocytic leukemia is best treated with adrenal cortical steroids.

Treatment of Acute Leukemia

The treatment of acute leukemia is so different from that of chronic leukemias that an accurate differentiation between these two must be made before treatment can be instituted. Roentgen therapy, radioactive phosphorus, and urethane do more harm than good.

Probably treatment of patients with acute leukemia does not result in any significant increase in life span after the onset of symptoms. Nevertheless, moribund patients treated by modern methods live to enjoy temporary improvement for several weeks or months, and there is always the hope and possibility that a fairly long-lasting remission may be induced. A defeatist attitude must not be assumed; these patients should be treated.

The three types of compounds that produce remissions in acute leukemia are folic acid antagonists (aminopterin), 6-mercaptopurine, and ACTH or cortisone. With any of these agents, relapse occurs and drug resistance develops. However, an infinitely better response is obtained in the child patient than in the adult patient. Best results are obtained in acute lymphoblastic leukemia. In acute monoblastic leukemia only supportive measures are of any value.

1. *Aminopterin (4-aminopteroylglutamic acid)*

This is the most outstanding of the folic acid antagonists advocated for the control of acute lymphoblastic leukemia. In a few cases, dramatic improvements have resulted. The drug is given orally in daily doses ranging from 0.25 milligram to 1 milligram for several days to several weeks. Therapy is discontinued on resumption of normal blood and marrow pictures, or the development of toxic lesions which consist of white, well-demarcated, mucous-like patches and ulcers in the soft tissues of the mouth and intestinal tract.

2. *Cortisone and ACTH*

These hormones have produced dramatic temporary improvement. If a remission can be produced with cortisone and ACTH, it can often be prolonged with 1 milligram of aminopterin a day.

3. *6-mercaptopurine*

This anti-metabolite produces temporary remissions in young adults suffering from acute leukemia. It is given orally in daily doses of 2.5 milligram per kilogram of body weight.

Recent reports suggest that in children, therapy with cortisone and aminopterin should be tried before 6-mercaptopurine.

If the patient is acutely ill, therapy should be initiated with ACTH and cortisone since the antimetabolites require at least three weeks to induce a remission. Once a remission has been induced or the acute emergency is passed, or if initially the patient was not in a critical condition, aminopterin (in young children) or 6-mercaptopurine (in those over 10 years of age) should be employed.

Supportive Measures:

i) Blood transfusions should be given for severe anemia. Hemopoetic agents are useless; folic acid is harmful.

ii) Antibiotics are used to control secondary infections.

iii) Little or nothing can be done for the severe thrombocytopenia and hemorrhages that accompany the disease.

Under therapy, many children can lead happy lives for the duration of their illness, whereas the untreated patient may suffer many painful complications.

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Agranulocytosis

Douglas O. Manners, '56

INTRODUCTION

Agranulocytosis is a disorder of the blood characterized by a reduction in the number of granulocytes and which may also include a decrease in the absolute number of other types of leukocytes.

The term agranulocytosis, as suggested by Schultz in 1922, described a clinical entity that had previously been described by Brown in 1902 and Turk in 1907. The clinical picture had been described in detail by Brown and Turk but general interest had not been aroused until after Schultz presented six cases in 1922. Since then a large number of cases have been described and a more complete picture of the disease formed. Only in the more recent years has the relationship between agranulocytosis and certain drug administration been clearly shown.

This condition has come to be known under many different names; some of these include: agranulocytic angina, granulocytopenia, granulopenia, agranulosis, agranulocythemia, hypogranulocytosis, idiopathic, malignant or pernicious leukopenia and granulocytic hypoplasia.

ETIOLOGY AND INCIDENCE

The exact etiology is unknown. Agranulocytosis has been described in countries throughout the world, but the majority of the reported cases have been in the United States and Germany. The disease affects all classes with slightly increased incidence among the medical profession, including physicians, medical students and nurses. The white race is seemingly much more susceptible than the Negro population. The female rate is higher than the male, in a ratio of 2 or 3 to 1. The peak incidence occurs in the 35-45 year age group.

The majority of cases are acute in character, although recurrent and chronic cases have been described. There has been no evidence of spread by contact and no apparent seasonal incidence. Infection often accompanies the picture of agranulocytosis and positive blood cultures of various organisms have been found. However, it is strongly felt that infection is a secondary manifestation of the condition. Organisms cultured from the blood have been injected into animals in an attempt to reproduce the disease, but without success.

The role of drugs as etiological factors has been clearly shown by various investigators. Coal-tar derivatives, organic arsenicals and gold salts are among some of the known agents. Agranulocytosis has been produced only after prolonged use of these drugs. The blood picture is that of agranulocytosis and frequently associated with thrombocytopenia and anemia.

One of the greatest offenders is a drug called amidopyrine ("Pyramidon"). It was used extensively in Europe until 1933 in the treatment of arthritis. Cases have been reported in which agranulocytosis was produced after a single dose of this drug and often proved fatal.

Other drugs causing agranulocytosis include dinitrophenol and certain sulfonamide compounds. The abnormal blood picture may be transient but a decrease in the number of granulocytes has been clearly shown. The course of the drugs is usually one of long term.

Cases of agranulocytosis have been reported in people who have taken thiouracil in the treatment of hyperthyroidism; tridione in the control of convulsions; certain antihistaminics (pyribenzamine and methaphenilene) and chloramphenicol in the treatment of pyogenic infections.

Within the past year, phenylbutazone ("Butazolidine"), used in the treatment of arthritis, has been reported to cause agranulocytosis. Recently, chlorpromazine ("Largactil") has been proven to cause a few cases of agranulocytosis.

Several cases of idiopathic agranulocytosis have been reported without a history of drug therapy. A definite etiological agent might have been discovered in some of these cases if the history and investigation had been more thorough.

PATHOGENESIS

It has been suggested by Kracke that a benzene ring with an attached "NH" or "NH^2" group produces an oxidation product which in turn produces a leukotoxic effect. It has been postulated that these toxic drugs may produce their effect by interfering with certain enzyme systems in the tissues.

In association with agranulocytosis, certain drugs frequently cause other signs such as edema, rash, urticaria and an asthmatic response. These manifestations have suggested the possibility of an allergic process. Tests to produce an antibody against amidopyrine in the hypersensitive individuals have been performed with negative results. Scratch tests, patch tests, intradermal tests and transfer tests have been essentially non-contributory to the theory of an allergic process.

The primary disturbance in the bone marrow in agranulocytosis is a deficiency of juvenile and segmented neutrophilic leukocytes; thus, a "maturation arrest" beyond the stage of myeloblasts. However, it is unlikely that this is the only factor because a leukopenia may develop within six hours after a dose of amidopyrine. Peripheral destruction of polymorphonuclear leukocytes or "pavementing" of leukocytes to the capillary endothelium must be acting as well to produce the granulocytic deficiency. Thus, the exact mechanism or mode of action remains a complex picture with a disturbance of the biochemistry of hemopoietic tissue the basis of the pathogenesis.

CLINICAL PICTURE

The onset may be sudden with general malaise, high fever, chills, rapid pulse and often stomatitis. The patient may then have relatively few symptoms except for prostration and fatigue. During this stage leukopenia results, particularly granulocytopenia. The patient may then become jaundiced, have gangrenous ulceration of the gums, tonsils, soft palate, lips, pharynx or buccal mucosa. Less frequently the skin, nose, vagina, uterus, rectum or anus are involved. There may be splenomegaly. Infection soon develops, due to lowered resistance in the absence of granulocytes. Bronchopneumonia or a septicemia usually causes a fatal termination.

Recurrent or cyclic cases have been recorded in which the acute attacks have been followed by asymtomatic intervals of weeks or months with an essentially normal leukocyte count. After the second or third attack the outcome is usually fatal. In the so-called "chronic" cases, the periods of a relatively normal leukocyte count are followed by attacks of malaise, headache, dizziness, fatigue and prostration but may occur without fulminating angina.

Laboratory Findings

(1) *Blood Picture*

The predominant finding is that of granulocytopenia but an associated decrease of the other leukocytes is usually

found. In acute cases, the count is initially less than 2000 per cu.mm. and then frequently drops to less than 1000 per cu.mm. Cases have been recorded with white counts as low as 50 and a complete absence of granulocytes. The granulocytes may have a pyknotic nucleus with vacuolated cytoplasm containing poorly stained granules. The presence of myelocytes in the blood only occurs after recovery begins. The lymphocyte is the predominating leukocyte found in the blood smear; occasionally, a relative increase in the monocytes is observed.

In the recurrent or cyclic forms of agranulocytosis, the leukocyte count rarely drops below 2000 per cu.mm. and the granulocytopenia is less pronounced.

In the typical case there is no anemia or thrombocytopenia, and the bleeding and clotting times are normal. There is no variation in appearance of the erythrocytes or in the reticulocyte count. However, the sedimentation rate is greatly elevated and the icteric index may be increased.

(2) *Bone Marrow*

The examination of the bone marrow shows normal erythropoietic tissues with a normal number of megakaryocytes. The microscopic picture may be one of moderate hypoplasia or of hyperplasia. The outstanding feature of the marrow is the lack of granulocytes which include not only polymorphonuclear cells but also the metamyelocytes and the myelocytes. An increase in the plasma cells, lymphocytes and reticulum cells may be seen but is not striking.

(3) *Urine*

There may be a trace of albumin but the urine is otherwise normal.

(4) *Cultures*

Blood cultures are often positive for a great variety of organisms. The current opinion is that these are secondary invaders due to the lowered tissue resistance in the absence of granulocytes.

Blood cultures often contain upper respiratory organisms.

DIAGNOSIS

The early symptoms of agranulocytosis simulate many other conditions so closely that it is often difficult to diagnose the condition before a septicemia has developed. It is essential that a physician be aware of the condition when any drug known to produce agranulocytosis is used and he should therefore be suspicious of any unusual symptoms. White blood cell counts should be done on these patients receiving the drug at least twice each month during therapy.

DIFFERENTIAL DIAGNOSIS

When local symptoms in the buccal cavity or a pharyngitis are present it is essential to differentiate the cause. In the majority of infections of the oral cavity and pharynx, leukocytosis is found. In other conditions such as typhoid fever, rubella, rubeola and undulant fever that present a leukopenia, the more gradual onset, and the characteristic signs and symptoms distinguish them from agranulocytosis. In any condition with a leukopenia it is unlikely that the leukocyte count would reach as low a level as found in this particular disease.

Some of the blood dyscrasias present a leukopenia; acute "aleukemic" leukemia and aplastic anemia can be recognized by the appearance of an anemia and thrombocytopenia. Leukemia often presents with immature leukocytes in the blood and adenopathy and splenomegaly. In infectious mononucleosis, extreme leukopenia is unusual; the lymphocytes are atypical and there is a positive heterophil antibody test (Paul-Bunnell Test).

PROGNOSIS

Before the advent of sulfonamides and antibiotics, the mortality in agranulocytosis was between 75 - 90 per cent and was greatest in elderly patients. The outcome is very poor if the patient becomes drowsy, confused, has profound prostration, jaundice, necrosis of the skin and a leukocyte count below 1000 cu.mm. with the absence of all granulocytes.

Death usually occurs from secondary complications such as sepsis, pneumonia or hemorrhage following necrosis.

Any improvement in the condition is manifested by the appearance of leukocytes of the granular series in the blood; myelocytes are the first to appear and then the metamyelocytes with myeloblasts on occasion. The segmented neutrophils are the last to appear. The appearance of monocytes that persist is thought to be a favorable prognostic omen. The leukocytic reaction may be marked and rapid with a leukocytosis of 15,000 per cu.mm. most often found.

MANAGEMENT

The actual management is difficult because many cases are extremely ill before any treatment is initiated or the patient is dead before any benefit can be derived. In many cases more than one remedy is used and so it is often difficult to evaluate which one actually produces a beneficial effect. Some observers report good results with certain drugs but other investigators have not been able to reproduce their findings.

A. Prophylaxis

The most important single factor in the treatment is caution in the use of any drug or related drugs capable of producing agranulocytosis. If the drug has been proven to cause the condition, the physician should be on the lookout for any leukopenia while the treatment is being carried out. The drug (or drugs) should be immediately stopped if granulocytopenia presents itself. The structural formula should be examined and if the substance contains one or more "benzamine" groupings, the possibility of agranulocytosis should be seriously considered.

B. General Care

Symptomatic treatment is essential and of great importance. The diet should be adequate with a liberal vitamin supplement. The possibility of any secondary infection should be minimized. The mouth and any local lesions should have meticulous care. The mouth and throat may be sprayed with a saturated solution of potassium chlorate; the ulcerated areas may be swabbed with a solution of copper sulfate (0.65 gms. to 30 c.c.).

C. Specific Treatment

1. *Antibiotics and Sulfonamides*

The use of antibiotics is perhaps the most beneficial specific agent. Penicillin is of great assistance in preventing an overwhelming sepsis. The actual reappearance of granulocytes probably occurs spontaneously after the offending drug has been removed. Although the sulfonamides have been known to cause agranulocytosis, they should not be withheld if they are not the offending agent. With the advent of penicillin and the broad spectrum antibiotics, however, it is seldom necessary to use the sulfonamides.

2. *Nucleic Acid Derivatives*

Of prime importance in agranulocytosis is the stimulation of granulocyte production. Compounds such as sodium nucleinate or pentonucleotide are no longer in use.

3. *ACTH and Cortisone*

These hormones have been reported to hasten recovery in some cases.

Their use is based on the possibility of a hypersensitivity reaction being involved in the pathogenesis. They constitute a double-edged sword, since they further depress resistance to infection. Antibiotic coverage must be maintained while the patient is being treated with either hormone. A satisfactory dosage is 50 mgm. of cortisone orally or intramuscularly four times daily, or 20 to 30 mgm. of ACTH by slow intravenous drip during an eight hour period each day.

The danger of using ACTH and cortisone must be weighed carefully in each case against the possible but uncertain beneficial effect on the agranulocytic process.

4. *Bone Marrow*

Yellow bone marrow and marrow extracts have been given orally with the hope of containing a marrow stimulating factor. The actual benefit produced has been questionable although the originators of this treatment report promising results.

5. *Blood Transfusions*

Transfusions of normal whole blood, blood from patients with leukemia or leukocytosis have been used, but with inconclusive results.

6. *Liver Extract*

Large doses of liver extract given intramuscularly have been used in an attempt to overcome any anemia present. The actual leukocyte formation (if any) has not been clearly demonstrated.

7. *Splenectomy*

Splenectomy has been recommended in some chronic cases of agranulocytosis.

8. *British Anti-Lewisite*

Where the granulocytopenia has been produced by arsenic or gold, B.A.L. has been given in doses of 1.5 mls. of a 10 per cent solution in oil six times daily for the first two days and then twice daily for another 8 - 10 days. B.A.L. has a pronounced beneficial effect in heavy metal poisoning and it is on this assumption that the substance is given in the treatment of this condition.

Conclusion

Many other measures have been tried in the treatment of agranulocytosis but most have seemed irrational. When the precise etiology has been discovered, then a specific form of treatment may be made available.

It must be emphasized that prophylaxis is the best "cure" and that drugs known to cause this condition should only be used as a calculated risk.

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Bleeding Disorders

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INTRODUCTION

Bleeding disorders are uncommon, but it is most important that they be recognized as such. Recognition may lead to diagnosis, and this in turn to an available treatment; above all, recognition may forestall tragic complications of surgery — "bleeders" are always poor surgical risks. A great deal has been learned about the mechanisms of blood coagulation since the classical theories were proposed. To the average physician this newer knowledge appears to be very complex; however, on further careful study it becomes apparent that the mechanisms of the various "bleeding" disorders are much better explained on the basis of this newer knowledge. Therapy based on replacement of demonstrable defects is daily becoming more effective.

One great difficulty in understanding blood coagulation, and even in reading about it, is terminology. Each factor has several names, and in at least one instance a single factor has been needlessly separated into two. The situation is fortunately ever more hopeful in that a more orderly pattern is evolving, and almost every month another piece of the puzzle is put into place.

It is not the purpose of this paper to elucidate the mechanism of blood coagulation, but rather to present a small amount of working theory, and to attempt to apply this to some of the more simple investigative techniques, with a view to the "screening" of bleeding problems.

The classical scheme of coagulation is of course rendered inadequate by present day knowledge, but it still serves as a useful framework upon which to build the more complex structure which is constantly being elaborated. There are three main steps:

1. *Platelets + foreign surface → thromboplastin (i.e. the generation of thromboplastin)*
2. *Thromboplastin + prothrombin + Ca+ + → thrombin (i.e. generation of thrombin)*
3. *Thrombin + fibrinogen → fibrin (clot) (i.e. generation of fibrin).*

Ordinarily this system of coagulation is held in abeyance, but when need arises it must become active and reach its purposed end quickly, perform its function, then bow out. The newer factors described help to explain how this is possible, how the clotting starts slowly, then accelerates, and finally that a clot does not propagate infinitely. The normal person is able to set up such a system of defence against bleeding which will protect him from all but the major injuries to blood vessels.

Vascular and Platelet Factors

It is apparent that when a tissue is injured, with laceration of blood vessels, a mechanism for hemostasis must be put into operation at once. The initial reaction of the blood vessels in the damaged area is constriction, which is mediated by axon reflexes from the nociceptive stimulus. The effect is to slow up the local circulation, and this may aid in the agglutination of platelets. The tissue injury also leads to liberation of thromboplastic substances. The agglutination of platelets leads to the release of a vasoconstrictor substance (angiotonin) which causes a generalized vasoconstriction to the area, and also to the release of thromboplastic substances and acceler-

ator factors of coagulation. The platelet and tissue factors form thromboplastin and a system is set up which results in a mechanical plug (clot) at the site of blood vessel injury. The clot eventually retracts, completing temporary hemostasis. Permanent hemostasis involves the organization of the clot, and its eventual removal (fibrinolysis) and recanalization of the blood vessel, with laying down of a new endothelial lining.

In discussing the vascular factors, it is apparent that despite any coagulation defect, if the vascular wall be intact spontaneous bleeding cannot occur. The corollary is also true, that with a perfectly normal coagulation system, but with a blood vessel wall defect spontaneous bleeding can, and does, occur. These vascular factors are understood only poorly. They include an intracellular cement substance, collagen fibres, fibrous tissue, endothelial lining, and neuro-humoral control. Scurvy is a good example of such a defect, in which ascorbic acid is insufficient for maintenance of the ground substance. A similar defect is probable in senile purpuras. Congenital defects of the small blood vessels probably explain the hemorrhagic diathesis of "vascular pseudohemophilia" (Von Willebrand's disease), and hereditary hemorrhagic telangiectasis, idiopathic hematemesis, and melena. In "primary" pulmonary hemosiderosis there is said to be an immunohematological factor.[2] It is postulated that the defect is in contractility of the vessels in the latter group of diseases. It is of great interest that primary pulmonary hemosiderosis and "vascular pseudohemophilia" manifest as episodic bleeding, with intervals in which bleeding times are normal.

Hypertensive individuals may also show purpura. Here there are several factors at play; frequently there is a defect of the walls of the arterioles, increased pressure opposes contraction and promotes flow through a defect. Such people may have a positive tourniquet test.

Inspection of the skin and mucous membranes in hereditary hemorrhagic telangiectasia shows dilated capillary and arteriolar loops which can be emptied—obviously if one of these is injured it is incapable of contracting sufficiently, and therefore prolonged bleeding ensues. In "vascular pseudohemophilia", by using special but simple techniques, one can see under the microscope the tortuous capillary loops in the nail beds (in vivo).[3] The diagnosis of these two disorders thus can be made quite easily if one takes an adequate personal and family history, and completes a few simple tests. The treatment of these congenital disorders has, to date, been unsatisfactory. Local pressure, if possible, is the best means of achieving hemostasis; as an alternative, cautery may be used. Diagnosis is, however, most important in order that necessary precautions may be exercised.

Thrombocytopenic purpura is a more complex situation, involving both vascular and coagulation defects. It is possible that some hormonal control exists in this situation since adrenal steroids and ACTH will usually control the purpuric manifestations without necessarily improving the platelet count.[4] As was mentioned above, the platelets, in addition to having an angiotonic effect, apparently release a thromboplastin precursor and possibly an accelerator of prothrombin conversion, and of fibrinogen conversion; as well they appear to release an "anti-heparin" substance. It is apparent then, that qualitative as well as quantitative platelet deficiencies may affect clotting. In thrombocytoasthenia (Glanzman's disease) there are normal numbers of platelets, but these are of bizarre morphology and are deficient in function.

Platelet deficiency manifests itself in several ways:

1. Purpura (i.e. spontaneous bleeding into skin and mucous membranes)
2. Prolonged bleeding time

3. Poor clot retraction
4. Diminished prothrombin consumption
5. Positive tourniquet test
6. Poor fibrinogen conversion.

Plasma and Serum Factors

There are present in the plasma several important coagulation factors. These may be divided into three groups:[4]

1. Thromboplastin antecedents
   (a) Antihemophiliac globulin (A.H.G.)
   (b) Plasma thromboplastic component (P.T.C. or Christmas factor)
   (c) Plasma thromboplastic antecedent (P.T.A.) — and probably several others
2. Prothrombin, calcium and fibrinogen
3. Accelerator factors (labile and stable factors)

As well, there is a system controlling the lysis of clot, which will be discussed later.

All of the above are present in the serum except fibrinogen, in concentrations related directly to their utilization during coagulation; there is also a stable component, serum accelerator, thrombin, (and an inactive, but potentially active, metathrombin complex).

Coagulation Theory

To discuss coagulation per se, there are three phases, as is mentioned in the classical theory. The first phase, a slow phase, involves platelet and tissue factors plus the plasma thromboplastin antecedents interacting to form thromboplastin. Defects in this phase are detectable by the thromboplastin generation test; this test, however, is not within the compass of the average laboratory.

The second phase (still a slow phase) depends upon the production of thromboplastin, which interacts with prothrombin, calcium, labile and stable factors to form thrombin. If there is failure of formation of adequate thromboplastin little thrombin will be formed, i.e. prothrombin will not be sufficiently used up and will remain in higher than normal levels in the serum. This is the basis for the prothrombin consumption test, i.e. the one stage prothrombin time of the serum is measured, using an exogenous source of fibrinogen. A diminished prothombin consumption, then, indicates a defect in phase one; thus it is a good screening test for the hemophiliac diseases, and for platelet deficiencies. This test can be carried out in any hospital laboratory.

Defects of the second phase show up as a prolongation of the prothrombin time. This finding usually indicates deliberate anticoagulation, or acquired hypoprothrombinemia from liver disease. It is also seen in association with obstructive jaundice. Defects of labile and stable factors also affect the prothrombin time, and one can usually deduce which factor is at fault by adding fresh plasma, stored plasma and serum.

The third (accelerated) phase of coagulation involves acceleration of the reactions just described, and pari passu reaction between fibrinogen and thrombin to form fibrin clot, with the aid of a platelet factor (Platelet factor No. 2). This whole reaction is autocatalytic, thus ensuring abundant factors. It appears that the basic trigger is the formation of a small amount of thrombin, which thus acts upon platelets, labile, and stable factors. It is apparent that once such an autocatalytic agency is set up, there must be "some way of stopping it", lest a complete clotting of the vascular tree occur. Owren has postulated an inhibitor substance against labile and stable factors. Fibrin clot actively removes thrombin, thus the main cog of the autocatalytic

mechanism is removed at an ever increasing rate until further fibrin formation must cease. The thrombin is later released at a slow rate so that it can be inactivated by anti-thrombin substances. Meta-thrombin is the name given the reversible end product of the absorption of thrombin by this group of substances.

Antithromboplastic Substances

Antithromboplastic substances are receiving prominent notice in the newer literature.[5] Tocantins has postulated that an antithromboplastic substance excess is the fault in hemophilia, rather than a deficiency of A.H.G., as is postulated by most other coagulationists. Another, but entirely different, thromboplastin inhibitor may develop in association with a variety of conditions:

1. Multiple transfusions (especially in hemophiliacs)
2. Pregnancy with an Rh incompatible product
3. Pemphigus
4. Lupus erythematosus disseminata

Etcetera.

In such situations there may be a resultant severe hemorrhagic diathesis.

Fibrinolysis

Once the clot is formed, it must of course be removed after it has completed its function; this is brought about by a fibrinolytic system.[5] The circulating plasma carries profibrinolysin, which may be activated by bacterial filtrates (such as streptokinase) and by normally occurring tissue fibrinolysokinase (which is particularly abundant in lung and uterine tissue). The active end product is fibrinolysin, which are inhibitors of clot lysis. The mechanism appears to have at least some endocrine control, in some way mediated through the pituitary gland, indeed ACTH or adrenal steroids may quickly diminish abnormal fibrinolytic activity. This phase of coagulation is mentioned because a severe bleeding diathesis may ensue from excessive fibrinolytic activity. This occurs in "stress" situations, hemorrhage, trauma especially to lungs, shock, extensive surgery, leukemia, and with carcinoma of prostate.

Screening Procedures

In screening a possible bleeding problem it is advisable to proceed stepwise, and to think, as much as possible, of the various phases of coagulation. There are a number of relatively simple laboratory tests which are of considerable help, if properly carried out and correctly interpreted. I shall attempt to describe these tests briefly, and to mention some of the other pertinent tests.

The history obtained from the patient is not a laboratory procedure, but it is a most important aspect of the investigation of a bleeding problem. One should enquire specifically about bruising tendency, bleeding from nose and gums, stools, urine, excessive bleeding from small abrasions, etcetera, and in females, menorrhagia. The family history is of great importance, as "bleeders" are usually well known in a family group, and it is important to know the sex of the "bleeders" and whether they are of maternal or paternal lineage.

Cases with a family history of both male and female bleeders (usually mild) whose only demonstrable defect of coagulation is a prolonged (variably so) bleeding time, and whose bleeding can be arrested only by local pressure, fall into the group of hereditary purpuras entitled "vascular pseudohemophilia" or Von Willebrand's disease. The diagnosis is confirmed by examination of the nail bed under oil and using a blue light—the characteristic tortuous arterioles are readily observed. This disease illustrates the importance of using standard tech-

niques for even such a "simple" test as a bleeding time. The Ivy technique[6] is a useful standard, and lends itself to comparisons. In this technique a manometer cuff is placed about the upper arm and inflated to 40 mm. of mercury maintained at that level, an avascular area on the volar surface of the forearm is selected, carefully cleaned with alcohol, and allowed to dry. With a sharp scalpel blade, a cut is made 2 mm. deep and 2 mm. long, and at this moment a stop watch is started. At 30 second intervals a piece of filter paper is lightly placed over the cut. In this way a permanent record is made. When no more blood attaches to the filter paper the bleeding time is recorded. The normal value varies from one-half minute to 6 minutes. This method is recommended over the Duke (ear lobe) method for 3 main reasons:

1. Permanent record is obtainable
2. It is standardized for venous pressure, and also for depth and size of the cut
3. Bleeding is easily controlled in this area (and in true bleeders this may be very important.

Prolongation of the bleeding time is seen in cases with a defect (primary) of the vascular wall, as in "pseudohemophilia", scurvy, and as well in cases with a secondary defect such as in thrombocytopenia and thrombocytoasthenia.

With the manometer cuff still in place as for the above test, one may carry out the tourniquet test for capillary fragility. In this procedure the forearm is carefully inspected for skin lesions which might be confused with petechiae, then the manometer is inflated to half way between the systolic and diastolic pressures and left at this level for 5 minutes (or up to 10 minutes if the patient can tolerate this). Various methods of recording the test are used; commonly, an area the size of a twenty-five cent piece is selected about 3 cm. below the antecubital fold. A count of petechiae is made in this area after the pressure has been released for 2 minutes. Any count above 5 is significant in men, above 10 in women. This test is positive in scurvy, senile purpura, and in thrombocytopenia when the platelet count is below 70,000 by the Dameshek method or 35,000 by the direct method.

The clotting time of whole blood is a procedure readily carried out in the office or at the bedside. It should be done carefully in order to avoid as many variables as possible.[7] Four clean dry test tubes $2\frac{1}{2}$" x $\frac{3}{8}$" are used, a clean venipuncture is made with a sharp #19 gauge needle, and a small quantity of blood is withdrawn. The tourniquet is then removed, a paraffined or siliconized syringe is attached to the needle, and 4 cc. of blood are withdrawn gently, at which time the stop watch is started. 1 cc. of blood is placed into each test tube, and these are kept at body temperature, preferably in a water bath, but if need be, this can be in a shirt pocket. The tubes are tilted at $\frac{1}{2}$ minute intervals, and the clotting time of each is that point when the clot holds together when the tube is inverted. The clotting time is the average of the four tubes. Normal value by this method is 5 to 10 minutes for ordinary tubes, and 18 to 25 minutes with siliconized test tubes. The latter is the more sensitive test, and detects a coagulation defect more readily — this is especially so in the hemophiliac group of diseases. These samples may be further used, for the prothrombin consumption test, or they may be left in a water bath at 37° C. for 24 hours for investigation of clot retraction and fibrinolysis. Of course, the observation of the clot gives at least some idea of the adequacy of the fibrinogen level. The clotting time is usually abnormal in the hemophiliac group, in cases with idiopathic or induced anticoagulants, extreme fibrinolysis, and in cases with gross deficiencies of prothrombin and its allied accelerators.

The second phase of coagulation is observed by the estimation of plasma prothrombin. This can be carried out in an office, but very few offices have the necessary equipment; however, it should be available in any clinical laboratory. It is not within the scope of this paper to discuss anticoagulant therapy, but it must be realized that this test is important in screening bleeders. Elevated prothrombin times are of course most commonly seen in anticoagulant therapy with coumarin derivatives (and it must be realized that these drugs may be taken unwittingly, for the purpose of malingering, or even with suicidal intent). In severe liver disease there may be a diminished prothrombin level (and also of factor VII)—this need be only slight to be of significance. Owren has described a bleeding diathesis caused by labile factor deficiency in which an alteration in prothrombin time is demonstrable. In obstructive jaundice, because of the poor absorption of vitamin K, there is an elevated prothrombin time, which can be corrected by parenteral administration of vitamin K—and indeed this may be a useful test of liver function and a tool in the differential diagnosis of jaundice. In hemorrhagic disease of the new born there is a prolonged prothrombin time which can be corrected by parenteral administration of vitamin K. The exact mechanism of this defect has yet to be elucidated, but it does appear that the prophylactic use of vitamin K has cut down the incidence of this disease, so presumably there is a defective absorption of vitamin K rather than poor utilization of it.

To backtrack for a moment to the first phase of coagulation, this phase is observed by the thromboplastin generation test[8] which is not easily carried out, and by the prothrombin consumption test[9] which is readily performed. In this latter test, blood is allowed to clot under standard conditions, and after a set period of time the prothrombin level of the serum is measured. Thus if thromboplastin is deficient, prothrombin will not be consumed to a normal extent in clotting, and hence will remain at high levels in the serum. This test then is abnormal in diseases with quantitative and qualitative defects of platelets, and in the hemophiliac group of diseases.

The platelet count may be difficult to perform in the office or even in a laboratory where it is an infrequent test, but a good substitute is the examination of a carefully made and well stained blood smear, preferably on matched coverslips. Ordinarily one sees one or several platelets in almost every oil immersion field, whereas in thrombocytopenia, several fields must be viewed before a single platelet is observed. The smear also permits morphological study of the platelets. Thus the stained blood film is an important, and easily carried out, screening test.

Fibrinogen estimations are difficult, but observation of the clot is helpful, and more recently a simple screening test for fibrinogenopenia has been made available commercially—this is called "Fibrindex"—and should prove to be very useful and time saving.

Because of the recent publicity about hemorrhagic diathesis in association with fibrinolysins,[5] I shall make brief mention of this subject. Fibrinolysis is seen in many circumstances such as:

1. Pregnancy
2. Hemorrhagic shock and trauma (especially to chest)
3. Extensive surgery (again especially to chest)
4. Premature separation of placenta (here there is another mechanism of intravascular clotting because of thromboplastic embolization in many instances).
5. Leukemia
6. Liver disease, especially cirrhosis

7. Transfusion reactions

8. Metastatic carcinoma of prostate.

The detection of fibrinolysis is exceedingly simple. A sample of blood is left to clot in a clean dry test tube at 37° C. for 24 hours, and is observed at regular intervals. If there is lysis of the clot before the end of 24 hours, there must be a fibrinolysin present. If, on the other hand, no clot forms, there must be complete afibrinogenemia, or a circulating anticoagulant. If the latter be the case, addition of this person's plasma will prolong the clotting time of normal whole blood.

Comment

This discussion has of needs been rambling. I have attempted to deal with the generalities of blood coagulation, with a view to clarifying some of its "mysteries", and to present what is, I hope, an easy plan for use in screening "bleeders". To recapitulate, the history re personal and family bleeding tendencies is all important. The bleeding, clotting, and prothrombin times (of both plasma and serum), examination of a well stained blood film, and observation of the clot, are some of the important laboratory steps. If the findings are properly interpreted, one can determine at least whether or not a bleeding problem exists, and possibly why it exists and what can be done about it.

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Hemophilia and the Related Disorders

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INTRODUCTION

Hemophilia has been defined as a clinical disorder characterized by a tendency to bleed and by a prolonged clotting time of whole blood which is strongly familial and is almost exclusively present in males. Our increasing knowledge of the mechanism of the coagulation of blood has led to the discovery of syndromes almost indistinguishable from classical Hemophilia, but which are amenable to differentiation and characterization by special laboratory studies. This paper is intended to discuss classical Hemophilia, which shall arbitrarily be referred to as Anti-hemophilic globulin (AHG) deficiency, Plasma Thromboplastin Component (PTC) deficiency or "Christmas Disease," and Plasma Thromboplastin Antecedent (PTA) deficiency.

PATHOLOGICAL PHYSIOLOGY

Two major theories have been advanced to explain the etiology of the bleeding in Hemophilia and the related disorders.

The first, and more widely accepted theory, states that Thromboplastin requires for its formation platelets, calcium, AHG (thromboplastinogen), PTC, and PTA. With classical hemophilia, the AHG which is required for thromboplastic activity is missing, deficient, or defective. It has been postulated recently that AHG must be activated by thrombin before it will react with platelets. Since thrombin is directly or indirectly responsible for the disintegration of platelets, and since in this condition only a minute amount of thrombin is formed, the platelets remain intact and defective hemostasis results. Similarly, the deficiencies of PTC and PTA will cause defective hemostasis. The varying degrees of severity can be accounted for by different degrees of insufficiency of these components.

The second theory has been postulated by Tocantins. He believes that thromboplastin formation requires two components: a cephalin-like lipid factor contained in platelets; and a plasma factor in the form of a conjugate of a platelet co-factor with a lipid inhibitor. He visualizes that the platelets are disrupted releasing the cephalin-like lipid and that the co-factor/lipid inhibitor conjugate is dissociated. The interaction of these components causes the formation of a cephalin-like lipid/co-factor conjugate which is plasma thromboplastin. If there is a disproportionate increase in the lipid inhibitor conjugated with the plasma co-factor of platelets, the amount of platelet material available is insufficient to overcome the excess of inhibitor and the interaction of platelet lipid and its plasma co-factor is prevented or greatly slowed, causing little plasma thromboplastin to be formed. This, Tocantins believes, is the fundamental defect of classical Hemophilia. According to this theory, various degrees of excess of the antithromboplastin activity above normal, result in the different degrees of severity of the condition. If there is a disproportionate decrease in platelet plasma co-factor with which the lipid inhibitor is conjugated, slower than normal thromboplastin formation results. This may explain the

pathogenesis of PTC deficiency since Tocantins believes that the platelet co-factor is probably PTC. Here, too, one gets various degrees of severity due to various degrees of insufficiency of the platelet co-factor.

GENETICS

Both Hemophilia and PTC deficiency are hereditarily similar. The trait is transmitted as a sex-linked recessive characteristic carried by the female and transmitted to the male. The gene is located in the X chromosome. If a hemophilic male ($\overline{X}Y$) marries a normal female (XX), the genotypes of their children will be $\overline{X}X$, who will be female carriers, and XY, who will be normal males. If a normal male (XY) marries a hemophilic carrier female ($\overline{X}X$), the genotypes of their children will be as follows: XX, a normal female; $\overline{X}X$, a hemophilic carrier female; XY, a normal male; and $\overline{X}Y$, a hemophilic male. It is possible that if a hemophilic male ($\overline{X}Y$) marries a carrier female ($\overline{X}X$), one of their children may have a genotype of $\overline{X}\overline{X}$, which would make her a hemophilic female. Such cases have recently been reported.

Only 50-75% of hemophilics give a family history of the disease. The reasons for this are threefold: first, an inadequate or inaccurate history may have been obtained; secondly, only female children may have been born for several generations; and finally, some consider that a gene mutation might occur in which the normal gene becomes a hemophilic gene.

PTA deficiency is transmitted as an autosomal, dominant trait. The disease may be transmitted by either males or females to male or female progeny.

PROPERTIES

Different fractions of the blood produce various findings with respect to AHG, PTC, and PTA activity. The plasma fraction contains all three factors. Normal serum does not contain AHG, but does contain PTC and PTA. The AHG activity is greatest in Cohn fraction I, whereas both PTC and PTA activity are greatest in fractions III and IV-1. Barium sulfate treated normal plasma and Seitz filtered normal plasma show both AHG and PTA activity but no PTC activity. Fractional separation of normal plasma by ammonium sulfate shows that AHG activity is greatest in the 0-25% fraction, while PTC activity is greatest in the 33-50% fraction, and PTA in the 25-33% fraction.

It is of great importance that AHG is consumed in the clotting process while PTC and PTA are not consumed, but rather appear to be potentiated by the clotting process and storage.

Differentiation of the various deficiencies may be carried out by mixing various fractions with the plasma of the propositus and noting the effect on the clotting time of recalcified plasma. For example, stored plasma will correct the clotting defect of PTC and PTA deficient plasmas but will not correct the clotting defect of AHG deficient plasma.

LABORATORY FINDINGS

Classically, Hemophilia is described as having a prolonged clotting time of whole blood. The other deficiencies also show a delay in clotting. The majority of cases with a clotting time of over 30 minutes and especially over 50 minutes have AHG deficiency. The majority of cases of PTC and PTA deficiencies have a clotting time of less than 30 minutes. Mild examples of these deficiencies may show a clotting time that is not prolonged. The prothrombin consumption test of Quick which estimates the available thromboplastic potency of the blood, shows that the prothrombin consumption is poor. Similar findings are found with PTC and

PTA deficiencies for this test. Here, too, very mild cases may present with an almost normal prothrombin consumption.

Several other tests have been shown to be abnormal with classical hemophilia. They are listed below.

1. Heparin clotting time is delayed.
2. Dilution clotting times are prolonged.
3. Recalcified plasma clotting time by either fast or slow centrifugation is increased.
4. Bleeding time for deep cuts (5 mm. or greater) is increased.
5. Thromboplastic activity test of Quick is positive.

The Thomboplastin Generation Test is a very sensitive test for deficiencies of AHG, PTC, and PTA. The three conditions may be distinguished readily by this test, as a rule.

Factors in the blood which are found to be normal in value are as follows:

1. Bleeding time of shallow cuts.
2. Capillary fragility as shown by the tourniquet test.
3. Clot retraction.
4. Platelet count.
5. Prothrombin level of plasma.
6. Fibrinogen level of plasma.
7. Calcium.
8. Accelerator globulins.
9. Serum Prothrombin Conversion Accelerator (SPCA).

Tests for naturally occurring anticoagulants are negative.

CLINICAL PICTURE

The principal manifestation of these conditions is the presence of a bleeding tendency. The bleeding is usually of a slow persistant type lasting for days and often initiated by trivial injuries. The bleeding tendency usually onsets early in life. Hemorrhage at circumcision is often the first sign. Later, bleeding or bruising after minor cuts, injuries, or tooth extractions may be excessive or even intractable.

The manifestations and severity vary from patient to patient but are often remarkably constant in any one person. Some live almost normal lives with little disability, while others, suffering from a severe form, die at an early age. It has also been shown that the degree of severity tends to be uniform throughout an affected family.

AHG deficiency usually causes the most severe bleeding tendency, while PTA deficiency usually has the least severe bleeding. There often seems to be some relationship between the degree of clotting time increase and the severity of the hemorrhage.

In AHG deficiency, it is commonly found that repeated hemorrhages into joints occurs with eventual production of arthritis, deformity, and limitation of movement due to formation of ankyloses. In this condition subcutaneous and intramuscular hemorrhages are frequent and often extensive and may be of a "spontaneous" nature. Hematuria may present in some people. Less commonly, asymptomatic gastrointestinal bleeding is found. Hemorrhage in the Central Nervous System is rare. Purpura is uncommon.

PTA deficiency seldom produces spontaneous bleeding. It is usually manifested after trauma, surgery, or commonly dental extraction. Hemarthroses and purpura are rare.

PTC deficiency lies in severity, between AHG and PTA deficiencies. Hemarthroses here are also uncommon.

DIAGNOSIS

The classical triad for the diagnosis of Hemophilia depended on three factors:

1. The characteristic type of bleeding beginning early in life.
2. The heredofamilial sex-linked transmission practically limited to males.
3. Retarded coagulation reflected in elevated clotting times and poor prothrombin consumption.

It can be seen that the above factors could not serve to differentiate AHG and PTC deficiencies. The most sensitive way of distinguishing these conditions involves the use of the Thromboplastin Generation Test. The final proof of the diagnosis of any of these deficiencies depends on the demonstration of the correction of the clotting defect by various factors as described above.

TREATMENT

Prophylaxis

The activities of the child who has a tendency to bleed must be tempered as much as possible. In adults, the patient must learn to avoid strenuous exercises and active participation in vigorous sports. Injury, no matter how trivial, must be guarded against.

General Measures

1. *Diet*—
   There should be an adequate intake of protein and Vitamin C.
2. *Pain*—
   Analgesics such as salicylates, codeine, or demerol should be used to control pain.
3. *Agents used to control hemorrhage*—
   (a) Whole Blood:
   Fresh whole blood is the method of choice in the treatment of AHG deficiency if the hematocrit is low. In Hemophilia, it has been shown that an AHG level of 10-20% of normal will assure adequate clotting. Fresh whole blood transfusions provide a source of AHG which will cause a temporary decrease in the clotting time, lasting for several hours. It makes no difference in the clotting time if 100 cc. of blood is used or if 500 cc. is used. Fresh frozen blood, reconstituted just before use, provides adequate AHG levels. With severe bleeding, 100 cc. of fresh citrated blood every 6 to 8 hours may be given until the hemorrhage is controlled. With PTC and PTA deficiencies, stored blood should be used in preference since as stated above, the effect of these substances seems to be potentiated by clotting and storage.

   (b) Plasma:
   With AHG deficiency, fresh whole plasma or reconstructed lyophylized fresh plasma should be used when the hematocrit is normal or high. If there is danger of serious hemorrhage, it may be necessary to provide a continuous supply of AHG by giving plasma every 3 or 4 hours or by a slow continuous IV drip. Once again, it is preferable to use stored plasma in the treatment of the patient who lacks either the PTC or PTA factors.

   (c) Globulin Substances:
   Plasma concentrates containing AHG such as Cohn fraction I may be given, but they are probably no better than simple transfusions since the body cannot store AHG. Cohn fraction I is of no value in PTC deficiency and of questionable value in PTA deficiency.

(d) Local Hemostatics:

For the treatment of bleeding external surfaces, bovine thrombin suspended in gelatin foam or freshly formed fibrin is the hemostatic agent of choice. Powdered tannic acid or powdered Russell viper venom may be used, but they are not as satisfactory.

4. *Psychological Implications*—

There must be a psychological readjustment on the part of the patient with regard to the necessary restrictions of activity. The readjustment must also involve the mother of the patient because she may develop a guilt complex knowing that she transmitted the disease to her child.

5. *Special Considerations*—

(a) External bleeding:

All the clot and other debris should be removed by gentle cleansing in order to get down to the oozing area. If necessary, the edges should be approximated, but without sutures. Bovine topical thrombin should then be applied promptly and liberally to the oozing area. A bandage should be applied to exert moderate pressure. Bovine thrombin should be used in preference to human thrombin because of the possibility of developing serum hepatitis.

(b) Hemarthroses:

These should be treated conservatively. At first cold is applied directly to the joint which should subsequently be kept at rest. Concurrently, active treatment should be undertaken to control the clotting defect. Later, heat may be cautiously applied to absorb the extravasated blood. Some people advocate aspirating the joint at this stage with installation of hyaluronidase into the joint cavity. A course of light massage, passive exercise, and then gradual activated exercises should be instituted to keep ankyloses at a minimum.

(c) Carious teeth:

These are also best treated conservatively. They should be filled in preference to extraction and no local anesthetic should be used. Teeth should only be extracted for intractable pain. If extraction is to be performed, the patient should be brought into hospital. A gutta percha or wax mold of the mouth and gums should be made in order to produce pressure around the tooth to be extracted. After the extraction, the socket should be dusted prophylactically with powdered thrombin and then the mold placed. Transfusions may be considered.

(d) Surgery:

Surgery should be avoided as much as possible. Septic conditions should be treated with antibiotics preferably, and cancer by irradiation. If surgery is absolutely necessary, the patient should be transfused before the operation with the proper substances in order to control the clotting defect. The transfusions should be carried on at intervals until the wound heals.

(e) Refractoriness to blood and plasma:

Here, cortisone and ACTH may temporarily diminish the refractoriness of the patient to blood and plasma. Transfusions with heparinized plasma may help also.

Summary

AHG, PTC, and PTA deficiencies have been discussed from the aspects of pathological physiology, differentiation of the various components, genetics, laboratory, investigation, clinical picture, diagnoses, and modern concepts of treatment.

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Abstracts

HEREDITARY SPHEROCYTOSIS

Can. Med. Association Journal,

January, 1956

John D. Stenstrom, M.D.

Hugh S. Ford, M.D.

The disease may be latent (the patient being asymptomatic), mild, or severe, in which case there is anemia, jaundice, and exacerbations of acute crises. The basic defect is the spherical shape of the red blood cells which invites destruction by the spleen, resulting in accelerated bile pigment metabolism, hyperplastic bone marrow, reticulocytosis, and anemia.

The spherocyte anomaly is an inherited Mendelian dominant characteristic, transmitted by either parent. A diagnosis should be made only when spherocytes can be demonstrated in the patient, and a parent, sibling, or offspring. Persistence of spherocytosis and increased osmotic and mechanical fragility are also essential characteristics.

The spleen is responsible for the rapid elimination of spherocytes. Splenectomy relieves the manifestations of the disease although the basic defect remains. The success of this operation depends upon the removal of all splenic tissue.

Excessive bilirubin excretion leads to the formation of gallstones in 75% of cases. Bilirubinemia is seen without bilirubinuria. Hemoglobinemia and hemoglobinuria are not seen in uncomplicated hereditary spherocytosis.

The pathogenesis of the crises in this disease is unknown, but is probably related to increased hemolysis, transient marrow aplasia, and splenic effects on the marrow.

The management of the crises as advised by some is multiple transfusions and early splenectomy; others urge caution in the use of transfusions because of severe reactions. Some defer both transfusion and splenectomy in hopes of a remission.

—Robert J. Tuttle, '56

ERYTHROBLASTOSIS FETALIS

Neva M. Abelson

Post graduate Medicine

Vol. 18, No. 4, October 1955

Two etiologic agents manifest as two equally common forms of hemolytic disease of the newborn.

(1) *ABO Erythroblastosis*:

One fourth of all babies possess erythrocytes that are incompatible with the mother's serum, but the baby which develops hemolytic disease has group A cells while the mother must have group O cells. The disease usually is mild, but if the serum bilirubin approaches 20 mgm%, exchange transfusion with fresh group O cells is indicated.

(2) *Rh Erythroblastosis*:

One in seventeen Rh negative females become sensitized during pregnancy. Hemolytic disease may ensue.

Treatment

(1) *Prophylaxis*:

Every Rh negative female should have three Rh antibody tests during pregnancy; at 16 weeks (base line), 30 weeks and 35 weeks. Rising titer suggests hemolytic disease.

In the event of intra-uterine death three potential dangers confront the mother: (a) emotional shock, (b) hypo-proteinemia as the result of rapid polyhydramnios and (c) disturbances of coagulation with possible serious hemorrhage.

(2) *Definitive*:

(a) interruption of pregnancy at the 37th or 38th week, if the husband is homozygous, there is a history of incompatible blood transfusion and the anti Rh titer is greater than 1:64. Exchange transfusion prevents kernicterus in the baby. (b) normal delivery and immediate exchange transfusion with packed group O cells. This with re-exchange transfusion controls fetal blood volume and anemia.

The criteria for exchange transfusion is to seek justification for withholding it.

—Bill Hogg, '57

Clinical Cases

W. P. Barton, M.D., F.R.C.P. (C)

A thirty-eight year old white, married, housewife with three children was referred to Victoria Hospital, London, for treatment of leukemia. The patient indicated that she had not felt well for the preceding six months, during which time her conjunctivae and skin became yellow and pallor was superimposed as well. The urine had been perhaps a bit darker but the stools had remained normal in color.

At age 16, this patient had begun to have bouts of jaundice which were painless. Eventually pain in the right upper quadrant supervened and led to an operation on the gall bladder, at age 34. Following this, jaundice continued to occur sporadically but was painless. The patient's father and brother gave histories of many bouts of painless jaundice.

On examination, there was fairly marked pallor and mild icterus. There were no fundal changes, no palpably enlarged lymph nodes and no bone tenderness. The spleen tip was palpable 9.0 cm. below the left costal margin in the midclavicular line on quiet breathing.

Laboratory Examination

Hemoglobin—9.0 Gm. (N 12 - 16 Gm.)

White count—14,500 (N 5 - 10,000)

Reticulocytes—12.5% (N 0.5 - 1.0%).

Examination of smear of peripheral blood:

normal differential

many small dense red cells with no area of central pallor: many large cells

platelets numerous.

Osmotic fragility of red cells—increased.

Diagnosis

Hereditary Spherocytosis.

Comments

This disease is commonly called familial alcholuric jaundice, which is less accur-

ate than the term hereditary spherocytosis because some of these patients do not have jaundice and have only the mildest anemia. The diagnosis can be suspected by history and confirmed usually by simply looking at a well-prepared smear of peripheral blood.

Splenectomy is curative. The red cell abnormality persists but the red cell survival time returns to the normal range once the spleen is removed. If this procedure is carried out at a sufficiently early age, it is likely that cholelithiasis might be circumvented.

Twelve-year-old girl was admitted to hospital because of a generalized purpuric eruption, ready bruising and epistaxes of one week's duration.

Three weeks previous to admission the patient and two siblings, as well as other children at school, had had measles.

On examination there were no abnormal findings except for the numerous petechiae and bruises, which had no predilection for any particular area. The spleen was not palpable.

Laboratory Examination

Hemoglobin — 13.0 Gm. (N 12.0 - 14.0 Gm.)
W.B.C. — 8,500 (N 5 - 10,000)
Platelets — 26,000 (N 300,000).

Examination of smear of peripheral blood:

differential - normal
red cells - normal
platelets - rare.
Capillary fragility test - 3+
Bleeding time 20 min.

Examination of bone marrow:

Many megakaryocytes, few of which were forming platelets. No abnormal cells seen. Erythroid and granulocyte series normal.

Diagnosis

Acute Thrombocytopenic Purpura (post-infectious measles).

Comment

Acute thrombocytopenic purpura is almost always a self-limited disease, which requires no therapy unless active bleeding is in progress. Even then, splenectomy is not advisable.

This child made a quite uneventful recovery and, at the end of three weeks, had a normal platelet count.

A twenty-eight year old white married female was first seen at Victoria Hospital, London, because of excessive uterine bleeding, epistaxes and prolonged bleeding after a tooth extraction at age 26. At that time her platelet count was found to be in the range 50,000 - 80,000. In the two years following her first admission she had bruised readily, but had not had any alarming blood loss. Consistently during that time, her platelet count remained subnormal. The bone marrow was normal. The spleen was not palpable.

It was decided that definitive therapy should be undertaken.

Accordingly, after pre-operative preparation with cortisone and transfusion with blood from siliconized apparatus, splenectomy was performed.

The spleen was of normal size and microscopically showed no lesions. The platelet count was normal within several days and has remained so for a period of 9 months.

Diagnosis

Chronic idiopathic thrombocytopenia.

Comment

Chronic idiopathic thrombocytopenia is a different disease from the acute form. By definition, spontaneous cure is rare. Splenectomy offers a 70-80% chance of cure. Why 20-30% fail to benefit from the operation is not known, nor can one predict in advance which patients will respond.

As a rule, cortisone or related adrenal steroids will elevate the platelet count in these patients while it is being administered, but the count reverts to low levels on discontinuing the drug. A splenectomy seems to be a much more definite measure and is without any of the unpleasant side effects of prolonged steroid therapy.

List of Recent Accessions

December 1, 1955 to February 1, 1956

The Library of the Medical School contains about 50,000 volumes, all fully catalogued, and is regarded as one of the best working collections of its kind in Canada. It is particularly rich in complete files of the more important medical journals. The books are on open shelves and students have access to all books and current journals.

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